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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,461	02/17/1999	FRANCIS THOMAS BOYLE	07164.0010	1092

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EXAMINER
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ART UNIT	PAPER NUMBER
1624	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/242,461	BOYLE et al.
Examiner	**Art Unit**
Brenda Coleman	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 4, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, and 7-17* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, and 7-17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claims 1, 3 and 7-17 are pending in the application.

This action is in response to applicants' amendment filed September 4, 2001. Claims 2 and 4-6 have been canceled, claims 1, 3, 7-9, 11 and 12 have been amended and claims 14-17 are newly added.

Response to Amendment

Applicant's amendments filed September 4, 2001 have been fully considered with the following effect:

1. With regards to the improper Markush rejection of claims 1, 3 and 7-13 of the last office action, the applicant's amendments and remarks have been fully considered but they are not persuasive. The applicants' stated that the "deletion of non-elected subject matter has overcome this rejection. However, the non-elected subject matter has not been deleted.

Claims 1, 3, 7-13 and newly added claims 14-17 are rejected as being an improper Markush grouping. For reasons of record and stated above.

2. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 1, 3 and 9-13 of the last office action, applicants' stated that "various forms of prodrugs are well known in the art and Applicants have incorporated by reference examples of such prodrugs". However,

> [t]he incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner

representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The term prodrug is of indeterminate scope in that they vary widely from drug to drug. It is not known which moiety of formula I would form the basis for the prodrug. Every ester, amide and carbamate in theory is biohydrolyzable, i.e. is capable in some degree of hydrolyses. Not to mention the many in vivo environments that this occurs in.

The applicants' further stated that "the proper inquiry is whether the experimentation needed to practice the invention is undue or unreasonable" and as is made clear in the MPEP, section 2164.06, citing *In re Wands*, 858 F,2d 731, 737, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". It is the Wands factors which are used to evaluate the enablement question. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman,* 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace substituted 3-mercaptopyrrolidine compounds. The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to

prepare the various compounds suggested by claims 1, 3 and 7-17. For example where are the starting materials for the preparation of compounds where the prodrug is methoxymethyl ester, pivaloyloxymethyl esters, phthalidyl esters, 1-cyclohexylcarbonyloxyethyl esters, 5-methyl-1,3-dioxolen-2-onylmethyl ester or 1-methoxycarbonyloxyethyl ester. A list of possible *in vivo*-hydrolyzable esters which includes only six is not sufficient to provide enablement for the assertion that every *in vivo*-hydrolyzable ester would be effective. While there are six *in vivo*-hydrolyzable esters mentioned on page 23, in lines 14-22, there is not one working example where the compounds of the instant invention were prepared. Additionally, there is no guidance as to the chemical reaction involved in the preparation of the *in vivo*-hydrolyzable esters. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claims 1, 3 and 7-13 and newly added claims 14-17 are is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons of record and stated above.

3. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 9 and 12, the applicants' remarks concerning the enablement of the inhibition of farnesylation of muatant ras

gene" is acknowledged but not found persuasive. The applicants stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement". Where structure sensitivity exists (in the pharmaceutical art) degree of testing must be representative of claims' scope. Note In re Fisher 166 USPQ 18; In re Surrey 151 USPQ 724. The journal article, i.e. Ayral-Kaloustian (1996), provided herein indicates that "targeting mutant Ras function has emerged as an exciting, novel, and viable alternative to traditional cancer therapy". Ayral-Kaloustian indicates that while "potency, specificity, and surprising lack of toxicity have been demonstrated", the clinical efficacy of these anticancer agents n humans bearing tumors with multiple genetic transformations remains to be proven". It is also indicated that "these agents appear to act mainly as cytostatic agents and will presumably need to be administered for prolonged periods, problems of toxicity and drug resistance may also be major hurdles to overcome.

Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds)

could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

Claims 9-13 and newly added claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons of record and stated above.

4. The applicant's amendments are sufficient to overcome the 35 USC § 112, second paragraph rejections labeled a), b), d), e), f), g), h), i) and j) in the last office action. However, with regards to the 35 U.S.C. § 112, second paragraph rejection labeled c), the applicant's failed to comment on the rejection of the last office action.

c) Claims 1, 3 and 9-13 are vague and indefinite in that it is not known how the -S-S- dimer can be made when the S atom of the pyrrole is substituted with a hydrogen atom is maintained for reasons of record and stated above.

5. With regards to the 35 U.S.C. § 103, obviousness rejection of claims 1, 3 and 7-13 by Leftheris, U.S. Patent No. 5,929,077 of the last office action, the applicant's amendments and arguments have been fully considered but are not found persuasive. The applicants' stated that "the Examiner has failed to specifically point out the basis of motivation for one of ordinary skill in the art to modify the prior art to derive the claimed invention". The structure of Leftheris referred herein is formula (I) where B is $-CH_2-$ or -C(O)-; B^2 is aryl or heterocycle; V and W are -

CH_2-; X is -SH; X' is $-NR^7$; m is 0 and n is 1. The mercaptopyrrolyl corresponds to the formula where X is -SH; X' is $-NR^7$ and n is 1. The genus of Leftheris in fact specifically teaches a substituent of the instant invention where B is $-CH_2-$; B^2 is naphthyl; V and W are $-CH_2-$; and m is 0.

Leftheris teaches structural isomers of the instantly claimed compounds. Examples 1, 4, 5, 6, 7, 8, etc. are position isomers of the specific species claimed herein, where mercapto is substituted to the pyrrole at the 3-position. Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homolog (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder , 563 F.2d 457, 195 USPQ 426 (CCPA 1977). There is no evidence of record that there is no real difference between the prior art and the invention.

E.g., Dillon 919 F.2d at 696, 16 USPQ 2d at 1904. See also Deuel, 51 F.3d at 1558, 34, USPQ 2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties").

Other structural similarities have been found to support a prima facie case of obviousness. E.g., In re May, 574 F.2d isomers); In re Wilder, 563 F.2d 457, 460, 195 USPQ 426, 429, (CCPA 1977) (adjacent homologs and structural isomers); In re Hoch, 428 F.2d 1341, 1344, 166 USPQ 406, 409 (CCPA 1970) (acid and ethyl ester); In re Druey, 319 F.2d 237, 214, 138 USPQ 39, 41 (CCPA 1963) (omission of methyl group from pyrazole ring).

A compound need not be a homolog or isomer of a prior art compound in order to be susceptible to a rejection based on structural obviousness. The name used to designate the structural relationship between compounds is not controlling, it is the closeness of that relationship. In re Payne et al., (CCPA 1979) 606 F2d 303, 203 USPQ 245. When chemical compounds have "**very close**" structural similarities and **similar utilities**, without more a prima facie case of obviousness may be made. In re Grabiak (CAFC 1985) 769 F2d 729, 226 USPQ 870.

Claims 1, 3, 7-13 and newly added claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leftheris, U.S. Patent No. 5,929,077. For reasons of record and stated above.

In view of the amendment dated September 4, 2001, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3, 7 and 9-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1, 3 and 9-15 are vague and indefinite in that there are two different definitions in claim 1 for the variable n.

b) Claims 7 and 16 are vague and indefinite in that there is an additional definition for the variable n.

c) Claims 1, 3 and 9-15 are vague and indefinite in that it is not known what is meant by the moiety N-(diC_{1-4}alkyl)carbamoylC_{1-4}alkyl) which has an unmatched parenthesis.

d) Claims 11 and 12 are substantial duplicates of claim 1, as the only difference is a statement of intended use which is not given material weight. Note In re Tuominen 213 USPQ 89.

e) Claims 10 and 14-17 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by inhibiting farnesylation of mutant ras gene. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when

administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in anticancer, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Mondays and Tuesdays from 9:00 AM to 3:00 PM and from 5:30 PM to 7:30 PM and on Wednesday thru Friday from 9:00 AM to 6:00 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner AU 1624
November 12, 2001